UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER

ART UNIT | PAPER NUMBER

14

DATE MAILED

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

12-04-92

☒ This application has been examined ☒ Responsive to communication filed on 8/20/92 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1, 3-15, 17-42, 47-49, 51-57 & 59-77 are pending in the application.
   Of the above, claims 67-76 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1, 3-15, 17-42, 47-49, 51-57, 59-66 & 77 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

15. Claims 2, 16, 43-46, 50 and 58 have been canceled in response to Applicants amendment.

16. Claims 1, 3, 18, 21, 35, 47, 51 and 52 have been amended.

17. New claim 77 has been added.

18. Claims 67-76 have been withdrawn as directed to a non-elected invention.

19. Claims 1, 3-15, 17-42, 47-49, 51-57, 59-66 and 77 are pending.

REJECTIONS WHICH STILL REMAIN

20. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

21. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

A) The disclosure has not enabled a person of ordinary skill in the art to use these methods in their broadest application, specifically for in vivo use in humans. Applicants have not disclosed to one of ordinary skill in the art how to use the protein as a pharmaceutical or therapeutic agent. There is an insufficient written description of the invention with respect to the in-vivo operability of the protein to enable one of ordinary skill in the art to use Applicant's invention for use in humans. In order to provide proof of utility with regard to antibodies and their uses, either clinical in-vivo or in-vitro data, or a combination of these can be used. However, the data must be such as to convince one of ordinary skill in the art that the proposed method is sufficiently established, see **In re Irons,** 340 F.2d 924, 144 USPQ 351 (CCPA 1965), **Ex parte Krepelka**, 231 USPQ 746 (PTO Bd. Pat. App. & Inter. 1986) and **Ex parte Chwang**, 231 USPQ 751 (PTO Bd. Pat. App. & Inter. 1986). When the method is directed to humans, as the claims read in broadest scope do, the data must generally be clinical, however, adequate animal data would be acceptable in those instances wherein one of

ordinary skill in the art would accept the correlation to human. Thus, in a recognized animal model for testing purposes. The specification fails to enable the claimed methods of treatment using the disclosed antibody for in-vivo use. Applicants have provided no in-vivo clinical data. Pharmaceutical therapies in the absence of in-vivo data are unpredictable. Waldmann teaches that effective therapy using monoclonal antibodies has been elusive and describes limitations of murine antibodies in the therapy of human diseases due to the pharmacokinetic properties of rodent antibodies in human and human anti-mouse antibody responses. Waldmann also indicates that hopes for antibody-based treatment methods engendered by in-vitro and animal model studies have not correlated well with in-vivo clinical trail results in patients. Therefore it does not appear that the asserted utility of the claimed method for treating humans would be believable on its face to persons of skill in the art in view of the contemporary knowledge in the art. See MPEP 608.01(p).

22. Claims 1, 3-10, 13-15, 17-24, 26-32, 35-42, 47-49, 51-57, 59-66 and 77 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

23. Claims 1, 3-10, 13-15, 17-24, 26-32, 35-42, 47-49, 51-57, 59-66 and 77 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to in-vitro regulation of T cell responses. See M.P.E.P. §§ 706.03(n) and 706.03(z).

24. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

and;

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

25. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office

obviousness-type double patenting as being unpatentable over claim 1-29 of copending application Serial No. 07/547,980. Although the conflicting claims are not identical, they are not patentably distinct from each other because they each are directed to a method of regulating T cell responses by modulating the interaction between CD28 and the B7 antigen.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

29. The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. *In re Vogel*, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

NEW GROUNDS FOR REJECTION

30. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

31. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

A) An application as filed must be complete in itself in order to comply with 35 U.S.C. 112; however this does not bar incorporation by reference. *Ex parte Schwarze*, 151 USPQ 426 (Bd. of Appeals, 1966). An application for a patent when filed may incorporate "essential material" by reference to (1) a United States patent or (2) an allowed U.S. application, subject to the conditions set forth below. "Essential material" is defined as that which is necessary to (1) support the claims, or (2) for adequate disclosure of the invention (35 U.S.C. 112). "Essential material" may not be incorporated by reference to (1) patents or applications published by foreign countries or regional patent

offices, to (2) non-patent publications, to (3) a U.S. patent or application which itself incorporates "essential material" by reference or to (4) a foreign application. See *In re Fouche*, 169 USPQ 429; 439 F.2d 1237 (CCPA 1971).

Nonessential subject matter may be incorporated by reference to (1) patents or application published by the United states or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications or (3) non-patent publications, for purposes of indicating the background of the invention or illustrating the state of the art.

The referencing application must include (1) an abstract, (2) a brief summary of the invention, (3) an identification of the referenced patent or application, (4) at least one view in the drawing in those applications admitting of a drawing, and (5) one or more claims. Particular attention should be directed to specific portions of the referenced patent or application.

The specification attempts to incorporate essential material by reference to a journal article and a patent application, see page 24, lines 6-12. It is suggested that Applicant incorporate this material into the specification.

32. Claims 19-24, 26-32 and 63-66 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to CD28 positive T cells. The claims are broadly drawn to any T cell this is clearly beyond the scope of the enabling disclosure.

33. Claims 3-8, 41, 42 and 47-49 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to a B7 fragment or derivative which represents:

A) An AA sequence containing residues from about position 1 to about position 215 of B7, corresponding to the extracellular domain of the B7 antigen.

B) A fusion protein as in (A) above and a second amino acid sequence corresponding to the hinge, CH2 and CH3 regions of human IG C-gamma-1.

34. Claims 9, 10, 56 and 57 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to immobilized B7 antigen on CHO cells. Applicants have not provided a sufficient enabling disclosure for any other immobilized B7 source.

35. Claims 13 and 14 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited

to use in vitro with out the addition of a cytokine. Applicants disclosure does not enable the use of the method in vivo or the use of the method in conjunction with a cytokine.

36. Claim 15 is rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to use of the method in conjunction with anti-CD-2. Applicants disclosure does not enable the use of the method with anti-CD-3

37. Claims 35-40 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the monoclonal antibody 9.3. The disclosure does not enable all possible antibodies to CD28.

38. Claims 47-49, 51-57 and 77 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to a CD28 receptor ligand that is B7Ig or monoclonal antibody 9.3. The specification does not provide an enabling disclosure for all possible receptor ligands.

39. Claims 1, 3-10, 13-15, 17-24, 26-32, 35-42, 47-49, 51-57, 59-66 and 77 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to inhibiting the interaction of CD28 positive cells with B7 positive cells in vitro. The claims are clearly outside of the enabling disclosure as being responsible for regulating all functional T cell responses, including production of cytokines, note specifically page 25, lines 25-35.

40. Claims 52-57 and 59-62 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to immune system diseases which are cause by the interaction of B7 with CD28 positive cells and cancers specifically responsive to inhibiting the B7/CD28 interaction. The disclosure does not enable the claims as being drawn to a treatment for all immune system diseases. Nor is the disclosure enabled for the treatment of all cancers.

41. Claim 66 is rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to inhibiting the interaction of B7 with CD28 positive cells. The use of the method as an immunosuppressant in conjunction with cyclosporine has not been enabled in the instant specification.

42. Claim 17 is rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to reacting CHO cells expressing B7 or fusion proteins with T-cells. The disclosure does not support the claims of reacting B-cells with T-cells.

43. Claims 19-22 and 59-62 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to a B7 antigen reactive ligand which is either:

A) monoclonal antibody BB-1 or a F(ab)2 fragment of said antibody, or

B) the CD28Ig fusion protein

The specification does not enable every possible ligand for the B7 antigen.

44. Claims 18 and 64 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the B7Ig fusion protein. The specification does not enable every possible soluble form of the B7 antigen.

45. Claim 25 is rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to monoclonal antibody BB-1. The specification does not enable every possible antibody to the B7 antigen.

46. Claims 26-32 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the CD28Ig fusion protein containing amino acid residues from about position 1 to 134 and a second amino acid sequence corresponding to the hinge CH2 and CH3 regions of human Ig C-gamma-1.

47. Claims 11, 12 are rejected under 35 U.S.C. § 103 as being unpatentable over Freeman et al. (CA) in view of Capon et al. (CE). Briefly the claims are drawn to a B7 fusion protein with the human immunoglobulin C-gamma-1. Freeman et al. teach the complete sequence of the B7 antigen see figure 3A. Freeman et al. do not teach a fusion protein of the B7 antigen to the human immunoglobulin C-gamma-1. Capon et al. teaches fusing human immunoglobulin C-gamma-1 to CD4 in order to prolong serum half life. Therefore it would have been prima facia obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Capon et al. to those of Freeman et al. to obtain a fusion of B7 with the human immunoglobulin C-gamma-1 in order to obtain a soluble B7 protein with a long serum half life, see entire Capon et al. document.

48. Claim 25 is rejected under 35 U.S.C. § 103 as being unpatentable over Yokochi et al. (CD). Briefly the claims are drawn to a monoclonal antibody reactive with the B7 fusion protein. Yokochi et al. teach the BB-1 marker on B-lymphoblasts, see abstract. This marker was later called the B7 antigen. Yokochi et al. produces a monoclonal antibody to this BB-1 marker called monoclonal antibody BB-1 see materials and methods. Therefore Yokochi et al. renders the claim completely prima facia

obvious to a person of ordinary skill in the art at the time the invention was made. A person of ordinary skill in the art would have been motivated to produce such an antibody to detect lymphoblastoid cells and cells of Burkitt's lymphoma which express the B7 antigen according to Yokochi et al. see title.

49. Claims 33 and 34 are rejection under 35 U.S.C. § 103 as being unpatentable over Aruffo et al. (AV) in view of Capon et al. (CE). Briefly the claims are drawn to a CD28 fusion protein with the human immunoglobulin C-gamma-1. Aruffo et al. teach the complete sequence of the CD28 molecule see figure 2. Aruffo et al. do not teach a fusion protein of the B7 antigen to the human immunoglobulin C-gamma-1. Capon et al. teaches fusing human immunoglobulin C-gamma-1 to CD4 in order to prolong serum half life. Therefore it would have been prima facia obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Capon et al. to those of Aruffo et al. to obtain a fusion of CD28 with the human immunoglobulin C-gamma-1 in order to obtain a soluble CD28 protein with a long serum half life, see entire Capon et al. document.

RESPONSE TO APPLICANTS ARGUMENTS

50. The rejection of claims 1-66 under 35 U.S.C. § 101 have been withdrawn in response to Applicants arguments.

51. The objection to the specification under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure, still stands. Applicants argue that the mouse studies shown in Exhibit 1 are sufficient to overcome this rejection. As pointed out in the rejection animal models can only be used if they are accepted models for Human therapy of which the mouse does not appear to be. Further enablement must be provided at the time the invention was made. Specifically as of the filing date of the application. There is nothing in the disclosure which supports in vivo use and therefore the rejection stands.

52. Claims 1, 3-10, 13-15, 17-24, 26-32, 35-42, 47-49, 51-57 and 59-66 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification, still stands.

53. The objection to the specification under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure, is withdrawn with respect to deposit issues

due to Applicants depositing the required materials.

54. The rejection of claims 1, 3-10, 13-15, 17-24, 26-32, 35-42, 47-49, 51-57 and 59-66 under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited in-vitro regulation of T cell responses. See M.P.E.P. §§ 706.03(n) and 706.03(z), still stands. Applicants refer to their previous statements, which point out Exhibit 1. Again enablement must be provided at the time the invention was made. There is nothing in the disclosure which supports in vivo use and therefore the rejection stands. It is suggested that the claims be limited to in vitro use.

55. The rejection of claims 15 and 21 are rejected under 35 U.S.C. § 112, second paragraph, has been withdrawn in response to Applicants amendments.

56. The rejection of claims 1, 15, 35-40, 51-52, 55, 56, 59, 60, 63, and 66 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Damle et al. has been withdrawn in response to Applicants amendments.

57. The provisional rejection of claims 1, 3-15, 17-42, 47-49, 51-57, 59-66 and 77 under 35 U.S.C. § 103 as being obvious over copending application Serial No. 07/547980, still stands. Applicants state that the co-pending application has been abandoned. However this is not the case to date. The rejection will be maintained until the co-pending application is abandoned.

58. The provisional rejection of claims 1, 3-15, 17-42, 47-49, 51-57, 59-66 and 77 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1-29 of copending application Serial No. 07/547,980, still stands. Applicants state that the co-pending application has been abandoned. However this is not the case to date. The rejection will be maintained until the co-pending application is abandoned.

59. The rejection of claims 1, 15, 35-40, 51-52, 55, 56, 59, 60, 63, and 66 under 35 U.S.C. § 103 as being unpatentable over Damle et al. has been withdrawn in response to Applicants amendments.

60. No claims are allowed.

61. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax

Art Unit 1806

Center telephone number is (703) 308-4227.

62. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donald E. Adams whose telephone number is (703) 308-0570. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

November 23, 1992

Donald E. Adams, Ph.D.

DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180
11/20/92